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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

BORIN, MICHAEL L

ART UNIT	PAPER NUMBER
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1631

DATE MAILED: 03/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/666,311	Applicant(s) DAHIYAT ET AL.	
	Examiner Michael Borin	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 October 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 4-9 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 4-9 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Amendment and response filed 10/17/2005 are acknowledged.

Claims 4,9 are amended. Claims 4-9 are pending.

2. Rejections not reiterated from previous Office actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112, second paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 4-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is applied for the following reasons.

B . Claim 4d): the phrase "ranking secondary library" is not clear. Specification does not discuss what kind of "ranking" is applied to the secondary library (ranking is discussed with respect to "primary libraries").

Response to arguments

Applicant argues that paragraphs [0032], [0033] provide sufficient support for applying ranking to secondary library similarly as it is disclosed for primary libraries.

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Applicant, however, withdrew from the citation the first sentence of [0032] which clearly directs it to primary library.

[0032] Some of these techniques result in the list of sequences in the primary library being "scored", or "ranked" on the basis of some particular criteria. In some embodiments, lists of sequences that are generated without ranking can then be ranked using techniques as outlined below.

Thus, there is no nexus in the cited paragraph between ranking of the primary and secondary libraries. The second cited paragraph, [0033], does not provide such nexus either.

[0033] In a preferred embodiment, some subset of the primary library is then experimentally generated to form a secondary library. Alternatively, some or all of the primary library members are recombined to form a secondary library, e.g. with new members. Again, this may be done either computationally or experimentally or both.

D (new) Claims 4 and 9 are amended to recite inputting into a computer of "primary sequences". At the same time the library of "primary sequences" is generated using an alignment program. It is not clear whether "primary sequences" in these two occurrences are the same or different (not all sequences can be aligned, so clearly not all of the first "primary sequences" will be a part of the "library of primary sequences" obtained by alignment program. Consequently, it is not clear, which "said primary sequences" are addressed later on in the claims.

E. (new). Claim 4 (e) is amended to recite that "at least sequence in the tertiary library is different from said primary library". This is not clear as the secondary library (i.e., the library preceding the tertiary library) is formed by a random combining of residues of a probability distribution table; what relation, if any, it has to the primary sequences?

Claim Rejections - 35 U.S.C. § 101/ 112-1

4. Claims 4-9 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The rejection is maintained for the reasons of record and further in view of the following.

Applicant argues that the resulting library (tertiary or secondary, in claims 4 and 9, respectively) “will contain an increased percentage of variants with desired property relative to library of random variants”. The claims, however, do not address any “desirable property”; thus, the use of the library of random sequences obtained by the claimed method will require further identification, and thus, further research. thus, the invention lacks both specific and substantial utility. Further, with regard to “increased percentage of variants”, all that claims as amended require from the tertiary library is to contain “at least one” sequence different from the primary sequences; therefore, in the extreme case of just one sequence being different, what is the difference (and thus utility) for the tertiary library? Applicant further asserts that the specific utility of the invention is the “ability to test a library of variant proteins”; however, the claims are not directed to testing library of proteins.

Examiner maintains that the instantly claimed method provide for generating a secondary library of as yet undetermined structure, function or biological significance which is obtained by a random combination of amino acid residues derived from a plurality of variant positions. Note that specification, paragraph [0103], guides that that

... in general, the variant positions and/or amino acid residues in the variant positions can be recombined in any number of ways to form a new library that exploits the sequence variations found in the primary library.

There is no evidence of record or any line of reasoning that would support a conclusion that the secondary library was, as of the filing date, useful for any industrial or any pharmacological uses. Until some actual and specific significance can be attributed to the secondary library or even the compounds present the library, an artisan would be required to perform additional experimentation in order to determine how to use the generated secondary library. Thus, there was no immediate "real world " utility as of the filing date. Because any potential pharmacological utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in any specific and practical form. The specification does not disclose substantial interpretation for the result; and none is known in the art. In order for generated library to be useful, as asserted, for any pharmacological use, there must be a well- established or disclosed claimed library correlation or relationship between the and a disease or disorder. The secondary or tertiary library of as yet undefined structure allegedly generated from the claimed method does not have a specific and substantial or real-world utility well-established utility.

For example, for a protein having 100 residues, and assuming that all 100 positions are considered to be "variant positions" and the residues are natural amino acids, the secondary library will be comprised of a random permutation of all 20 natural amino acid residues. Utility of such random library is not addressed neither in specification, nor in applicant's response. The above considerations addresses applicant's request

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to demonstrate why one of ordinary skill in the art would question the asserted utility of the invention.

Claim Rejections - 35 USC § 102 and 103.

5. Claims 4-9 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Topham et al. (J. Mol. Biol., 229, 194-220, 1993)

The claims are drawn to method for generating a library of scaffold protein variants comprising:

- a) generating library of sequences using an alignment program;
- b) generating a probability distribution of variant amino acid residues in a plurality of positions;
- c) combining residues from said probability distribution to generate secondary library;
- d) ranking the secondary library to generate tertiary library
- e) synthesizing protein variants from tertiary library of scaffold protein variants.

Topham et al teach method of modeling protein variants by comparing proteins in a protein families, calculating frequencies of occurrence and probabilities for selected residues, and applying smoothing and ranking functions. The method includes the steps of :

- a) generating library of sequences using an alignment program – see abstract, p. 195, last paragraph , p. 196 , section (a) and last paragraph ;

b,c) generating a probability distribution of variant amino acid residues in a plurality of positions and thus generating secondary library - see p. 196, last paragraph, p. 200, left column;

d) ranking the secondary library by applying two smoothing entropy-driven weighting functions – see , p. 200, section (d)

Topham reference does not teach synthesizing protein variants from the obtained library of protein variants. However, it would be *prima facie* obvious to one skilled in the art that the desirable end stage of any protein modeling is synthesis of proteins of interest; thus an artisan would be motivated to synthesize optimized protein variants obtained by method of Topham. Further, selection of PCR method to synthesize proteins would be obvious to an artisan as it is one of the main methods of protein synthesis, and selection of particular parameters of PCR would be obvious to an artisan as a part of routine selection of optimal parameters.

Response to arguments

Applicant argues that Topham fails to teach or suggest creating either a secondary or tertiary library of sequences. Examiner disagrees. Applicant's attention is directed to Table 5, and section e) on p. 215, as an example of the approach taught in the reference. There, a primary sequence is DRYDR is used to generate a probability distribution for residues in the positions of the primary sequence which generated a list of suitable fragments upon which to model the five residue loop DRYDR. Thus, the list of fragments considered to be suitable is viewed as "secondary library". When smoothing template was subsequently applied, some of the modeled fragments which have been excluded from the list of suitable were then included in the list because now

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they appeared to fit the ranking criteria. Thus, the latter, expanded, list is viewed as a "tertiary" library.

Further, applicant argues that Topham does not teach synthesizing protein variants. Applicant is reminded that the rejection of record is not an anticipation rejection under USC 102, but is rather is an obviousness rejection under USC 103(a), and that the latter limitation was addressed in the rejection of record.

Double Patenting

7. Claims 4-9 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4-8 of U.S. Patent No. 6,403,312. The rejection is maintained for the reasons of record.

The Terminal Disclaimer filed 10/17/2005 has been disapproved.

8. Claims 4-9 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-29 of copending Application No. 09/927790.

This is a provisional obviousness-type double patenting rejection.

Applicant has submitted earlier that this rejection would be addressed after the claim scope in this and the co-pending application is re-evaluated.

Conclusion

9. No claims are allowed

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D., can be reached on (571) 272-0718. The fax phone

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number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Michael Borin, Ph.D.
Primary Examiner
Art Unit 1631

mlb